UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM:

To: Julie Breeden-Alemi, DVM

From: Kevin Ulrich, Ph.D., Entomologist

Secondary Review: Pesticide Efficacy Review Committee (PERC)

Date: 6/23/2020

Subject: REBUTTAL TO DP 456609, 04/23/2020

THIS REBUTTAL REVIEW DOES NOT CONTAIN CONFIDENTIAL BUSINESS INFORMATION

Note: MRIDs found to be **unacceptable** to support label claims should be removed from the data matrix.

DP barcode: 457660
Decision no.: 558484
Submission no: 1051546
Action code: R340
Product Name: Hartz Reference 156
EPA Reg. No or File Symbol: 2596-187
Formulation Type: Pet Collar
Ingredients statement from the label with PC codes included:
Deltamethrin 4.0% PC: 097805

Application rate(s) of product and each active ingredient (lbs. or gallons/1000 sq ft or per acre as appropriate; and g/m^2 or mg/cm^2 or mg/kg body weight as appropriate): Apply one 4% deltamethrin collar (1 collar = 31 g (a.i. = 1.24 g deltamethrin/collar)) per dog, 12 weeks of age or older. Remove 2-3 inches from collar buckle. Reapply 1 collar every 6 months.

Use Patterns: Collar is registered for dogs to kill fleas and ticks for up to 6 months. Proposed use claims include repelling fleas and ticks for up to 6 months and repelling and killing mosquitoes for up to 6 months. Collar should be replaced every 6 months. For use on dogs 12 weeks and older only.

I. Action Requested: The registrant requested review of a rebuttal argument (MRID 51143501) in response to the previous review (DP 456609).

II. Background: The original DER (MRIDs 51018801, 51018802, and 51018803) did not support kills or repellant efficacy claims against adult fleas, ticks, or *Ae. aegypti* mosquitoes.

III. Rebuttal Summary:

Argument 1. *MRID #51018801 and 51018802 was classified as supplemental by the reviewer but we feel the information provided in the documents was extremely important background given the testing protocol. The protocol once accepted represents an asset which Hartz and the test laboratory developed using the European guideline as a basis for the testing since an EPA approved protocol did not exist. The protocol does discuss methods for evaluating the data which have been questioned by the reviewer.*

Agency Response 1. MRIDs 51018801 and 51018802 did not contain any efficacy data. The protocol outlined in these MRIDs was largely redundant as to what was included in 51018803. Alone, neither of these MRIDs would support the addition of repellent or kills claims on the product label and therefore, were classified as supplemental. Please note that your application package was submitted under PRIA category R340 for the purpose of adding label claims for invertebrate pests of public health or economic importance. This PRIA category excludes animal products submitting animal safety data for support of label amendments. While not required, if the registrant wishes to have a protocol reviewed by the Agency, they may submit one under PRIA category R272.

Argument 2. *Our study first, answers the question is there efficacy difference i.e., possible leaching of the active ingredient at different rates which could affect the efficacy and duration of the collar. The data was being run as stewardship issue even though EPA scientist apparently did not see a need to conduct this testing. This important point which EPA failed to address, should have been evaluated with an understanding that this discussion had taken place and that this data was extremely important to confirm a fact that EPA had accepted without scientific proof. Hartz has intentions of using both methods of manufacture and will use the data as confirmation that the manufacturing procedure whether extruded or injection molded will not affect the collar efficacy. The reviewer has made no reference to the importance.*

Agency Response 2. Thank you for this clarification. The cover letter for this submission did not discuss or allude to manufacturing differences between the test substances. Furthermore, neither the study justification nor test substance sections of the MRIDs mention trials being conducted to study leaching effects. If the registrant's intention was to bridge efficacy data between extrusion and injection molded manufactured collars, this should have been stated in the submission materials. The registrant's cover letter stated that the submission was "to support registration claims for repellency vs. fleas and ticks. The study also includes confirmatory data vs. mosquitoes (*Aedes aegypti*), a claim which was previously submitted via Fast Track, citing existing data." Therefore, the Agency conducted its review with the understanding that this application was to add new tick, flea, and mosquito claims to the label.

Argument 3. *Some of the efficacy evaluation did not begin at normal test interval. The Agency has already approved the collar kill claim, we believe it can be agreed that efficacy would trend closer to the pass/fail point with age; therefore, as a confirmatory point for efficacy extruded vs. injection molded we began looking at the study animals at the 3 to 6 month time vs earlier in the study for kill results.*

Agency Response 3: The Agency previously approved collar kill claims based on the citation of data. Whether previously cited tick and flea kill claims remain on the product label is left to the discretion of the Product Manager. However, data provided in this submission alone are insufficient to add flea and tick kill and repellency and mosquito claims to the product label. This study only provides evidence that the product can be effective at 3 to 6 months. Using the data provided from this MRID, we will not make assumptions about whether the collar is efficacious at repelling ticks and mosquitoes at earlier timepoints.

Argument 4. *The data developed in test groups 4 and 5, testing the collar with an oral and an oral alone were generated to demonstrate the efficacy and safety of the collar as a repellent. The data generated using the collar and oral is on the registered collar and should have been evaluated in the review. The registrant has submitted additional data on this study including evaluation of safety in support of a second deltamethrin collar EPA Registration No. 2596-188, MRID 51079500 and 51079501. The registrant's intention is to file a second amendment to register product with use of an oral.*

Agency Response 4: As there are no oral product claims being added to the amended label these product groups were not evaluated. We only evaluated data that would support the amended label claims. The registrant made no indication in the submitted application that reviewing that data was their intent. Additionally, dosing protocol must follow that on the product's Directions for Use or proposed label. As such, treatment using an oral product concurrently with the collar would conflict with the label and the MRID would be unacceptable. Note that the PRIA category under which this package was submitted excludes animal safety data for support of label amendments for animal products.

Argument 5. *The registrant in developing the study assembled a study which incorporated the data needed for registering the product using the fewest number of animals to get a scientifically sound study given the duration and cost of study. The registrant with more than 30 years experience has never had occasion where a reviewer did not review the entire study submitted. The information concerning the 3% collar was likewise generated to support registration of the reduced active label. The registrant has submitted a 3% collar which was withdrawn at EPA request since it lacked efficacy data. The registration was withdrawn to comply with the Agency request and the registrant will be citing this data with the submission this quarter. With the inclusion of the data the registrant will bear the expense of a single study review and more importantly respect the limited resources at the Agency by having them conduct only a single review vs. multiple reviews in the short space of 12 to 18 months. I do not believe the Agency system currently offers a registrant an option to review only part of a GLP conducted study.*

Agency Response 5: As mentioned previously, the reviewer evaluated data that would support the amended label claims. The submitted application contained no indication that reviewing data not supported by the label was the registrant's intent. Data for the 3% collar was viewed as extraneous information. Summaries of efficacy for the 3% deltamethrin collar (i.e., Group 6) are presented below in Tables 1, 2, and 3. Results for the 3% collar were similar to those of the 4% collars. Likewise, product performance data began 2 months after placement. While some flexibility could be given for longer duration collars, a standalone study should still have testing done at Day 3 and be fully efficacious by Day 14. Therefore, data for the 3% collar do not support kill and repellent efficacy claims against adult fleas or ticks for 6 months. As noted in the original DER, 6-month efficacy cannot be achieved by combining this study with new data showing efficacy for up to 2 months. For 6-month residual claims, data must be submitted for the full 6-month timeframe.

Table 1. Tick efficacy 24 hours after challenge

Species	**Day**	**% Mortality** Group 6	**% Repellency (dog collected)** Group 6	**% Repellency (crate collected)** Group 6
R. sanguineus	45	68.0	55.7	88.0
	92	71.8	63.3	**95.2**
	122	51.6	45.4	67.6
	182	68.3	62.1	**93.5**
D. variabilis	45	77.3	77.3	56.6
	92	70.1	68.6	88.5
	122	37.4	28.5	81.0
	182	55.3	50.1	83.8
I. scapularis	52	**98.6**	**95.8**	64.3
	99	**100**	**94.8**	42.9
	120	**100**	**100**	66.6
	190	**100**	**100**	61.0

Table 2. Flea efficacy 24 hours after challenge

Species	Day	% Mortality Group 6	% Repellency (dog collected) Group 6	% Repellency (crate collected) Group 6
C. felis	63	**94.4**	**94.4**	**97.3**
	107	**94.6**	**92.4**	**98.4**
	137	**97.5**	**96.6**	**98.7**
	191	**94.6**	**92.3**	87.4

Table 3. Mosquito Efficacy

Species	Day	% Anti-Feeding (@24 hours) Group 6	% Mosquito Mortality (@24 hours) Group 6	% Knockdown (@60 minutes) Group 6
Ae. aegypti	62	79.2	**100**	**96.2**
	69	81.7	**98.5**	88.5
	106	**93.6**	**99.4**	84.7
	136	86.8	**100**	**95.4**
	196	53.6	**89.7**	71.3

Argument 6. *Concerning the calculation of repellency for ticks and fleas the European Medicines Agency (14 July 2016) EMEA/CVMP/EWP/005/2000-Rev.3 "Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats" was used as a reference.*

Agency Response 6: The Agency concurs with the registrant that the repellency calculations based on the European Medicines Agency (EMA) Guidelines are acceptable.

Argument 7 *During each tick infestation throughout the study a total of 50 ticks with a balanced sex ratio (50% female: 50% male) were applied. That translates to a total of 25 females and 25 males per infestation. For repellency counts as outlined in Table 87, only female I.s. ticks were considered for calculations (in all groups). Using EPA's comment that a mean of 25% or greater retention is needed on controls, an average of 6.4 to 13.4 female ticks were seen on controls, which averages out to 25.6% to 53.6% retention.*

Agency Response 7: Thank you for this correction. We agree that retention rates of *I. scapularis* exceeded Agency standards. However, clarification of these results does not change the underlying issues, which was that the study only provided product performance data beginning 2 months after collar placement.

Argument 8. *Mosquitoes: It has been well documented in the literature, the repellent nature of pyrethroid. Deltamethrin, the active ingredient in the collar is a pyrethroid, with widespread use in malaria countries, and is used for the treatment of bed nets, screens and other areas to prevent transmission of disease. Many of these uses are approved by EPA since these claims are required to qualify for USAid funding; a similar Deltamethrin collar by Welmark, RF2253 Collar D Registration No. 89459-98 and other registered generics which are also "me-too" registrations are marketed as EPA registered products. One citation on available data in the literature is, Relative efficacy of Synthetic Pyrethroids impregnated fabric against mosquito under laboratory conditions: Ansari, MA, Kapoor N, Shermar VP; Journal of American Mosquito Control, 30 November 1998; 14(4)406-409, the data confirms the efficacy vs. 3 species of mosquitoes. Additionally, the registrant cited the same data used by its market competitors to support the mosquito claim which the Agency has not granted.*

The registrant developed the data on a single species to again confirm the fact that there are no differences associated with the method of manufacture i.e. injection molded vs. extruded, the data was not meant to substantiate a claim. The registrant's claims concerning mosquitoes should be approved immediately.

Agency Response 8: The conclusions in the original DER are based solely on the data presented in the MRIDs. Due to high mortality in control groups, the submitted data do not support repellent or kill efficacy claims against *Ae. aegypti*. Regarding the addition of mosquito claims to the product label using cited data, this is left to the discretion of the Product Manager.

Argument 9. *EPA defines repellents as any substance or mixture of substances intended for: preventing, destroying, repelling or the mitigating of a pest. What does this mean? The Hartz study evaluated the collar by looking at the activity at multiple time points. The study also measures the ticks and fleas at 4 and 24 hours for both its ability to repel but under the EPA definition which includes death as a form of repellency. There are numerous EPA registered products on the market where this broad definition of repellency has been used and a claim of repellency has been granted.*

Agency Response 9: We are unaware of the Agency using the above definition to describe repellents. This definition is more in line with the term "pesticide" defined in FIFRA 2(u). In the forthcoming *Product Performance Test Guideline OCSPP 810.3300: The Efficacy of Treatments Topically Applied to Pets Against Certain Invertebrate Ectoparasitic Pests*, EPA will be provided a concise definition of repellency similar to that in EMA guidelines. The EMA guidelines state that a "product with a repellent effect will cause the parasite to avoid contact with a treated animal completely and/or to leave a host."

Argument 10. *Addressing the above point about ticks, a review of the literature reveals that ticks, in particular deer ticks, the species tested, do not attach for 24 -48 hours. MJ Cook, in an article in the International Journal of General Medicine in 2015 wrote, it is frequently stated in the literature that the risk of attachment is extremely low in the first 24-48 hours, with some researchers claiming there is no risk of attachment. The reviewers claim that the study did not look for engorged ticks may be valid but based on the science the possibility the researcher would have found ticks is minimal if at all and has little or no effect on the statistical analysis in the study. The claim that the collar does repel not only meets the EPA definition and the science demonstrated in the study support the claim.*

Agency Response 10: Thank you for this information. The Agency will take this literature into consideration for future efficacy reviews and guideline development. The reviewer's statement indicating that the study did not supply engorgement or blood feeding data was informational only and not, in and of itself, the reason why the MRID was deemed not acceptable. In fact, the original DER noted in the conclusion that the collar may repel *I. scapularis* for 52 to 190 days after collar application. However, the study was not acceptable because assessments did not begin until 2 months after product application.

Argument 11. *At all counts, moribund parasites were classified as "live" for purposes of calculations. Following the protocol, the study does not deviate from other protocols and count moribund parasites in the living classification. The registrant does believe that following the EPA definition a moribund flea and/or tick has been prevented from biting and thus should be counted as being repelled. The possible recovery of these parasites and the ability to bite and transmit disease has been demonstrated and there is no evidence to dispute the fact that even if the parasite made a full recovery, the treatment which had effected the parasite would not have the same effect on the parasite a second time.*

Agency Response 11: Thank you for clarifying that "moribund" parasites were classified as "live" for calculation purposes. The mortality percentages noted in the original DER remain unchanged. As noted above, the Agency agrees with the registrant's original formula for assessing repellency (i.e., comparing mean number of live and dead ticks/fleas collected from dogs). For flea and tick repellency claims, moribund individuals are not relevant as arthropods would be placed into either "on animal" or "off animal" categories without consideration of life status.

Argument 12. *It has been discussed earlier, the reason for evaluations beginning at day 52 and later. Data on the effectiveness of the collar during its peak generation of pesticide is well documented by studies reviewed by the Agency and available in the literature, the registrant citing this data was given a 6 month claim along with a number of other generic collars in the market. It has also been demonstrated by the registrant and others that peak*

leaching of active ingredient from the collar occurs during the first months of collar application.

Agency Response 12: We are not aware of other submitted studies successfully demonstrating repellency for ticks and fleas using 4% deltamethrin collars. The Me-Too cited product (Reg No. 68451-1) does not list flea and tick repellency or mosquito kill claims. It does include tick and flea kill claims and mosquito repel claims for up to six months. For 6-month repellent claims, data must be submitted or cited for the full 6-month timeframe.

Argument 13. *This product was not efficacious against R. sanguineus or D. variabilis. Except on Day 45 for D. variabilis in Group 2, neither mortality nor repellency for either species reached the 90% threshold. Hartz agrees with this statement and is requesting a claim of repels deer ticks and transmission of Lyme disease.*

Agency Response 13: While several issues have been addressed by the registrant in this rebuttal including control retention rates (Argument 7) and attachment/engorgement (Argument 10), the registrant still needs to submit a full 6-month study for repellent tick claims or provide a citation for a previously accepted study. Additionally, in order to obtain general tick claims, all three required species should be tested. This ensures that there are supporting data against the major disease vectors in these groups. For dogs, testing in three species should be performed including the blacklegged tick (*Ixodes scapularis*), American dog tick (*Dermacentor variabilis*), and brown dog tick (*Rhipicephalus sanguineus*)

Argument 14. *Hart is claiming repels C. felis. The product was initially registered as a "me-too". The registrant cited existing data and label claims. The claim outlining 2-3 weeks before reaching maximum effectiveness has been developed using alternate data. The registrant again wishes to point out that in some cases evaluation did not begin until later in the study was because data already existed to substantiate claims, the study was seeking to demonstrate that the manner of manufacture did not affect efficacy and finally the registrant was seeking to minimize parasite infestation thereby reducing total number of dogs in study.*

Agency Response 14: As mentioned above, the registrant's intent to provide a confirmatory point between extruded and injection molded collars was not provided in the application. The Agency acknowledges that based on data and timepoints provided, there does not appear to be a difference in efficacy between the study's deltamethrin-only collars during the 2-6-month timeframe. The Me-Too cited product (Reg No. 68451-1) does not include flea repellency claims. It does include flea kill claims for up to six months. For 6-month residual claims, data must be submitted or cited for the full 6-month timeframe. While some flexibility could be given for longer duration collars, a standalone study should still have testing done at Day 3 and be fully efficacious by Day 14.

Argument 15. *Concerning the second assumption that engorgement [of C. felis] was not evaluated. We again call your attention to the full data compliment and the EPA definition of repellent i.e., mitigating and/or destroying. The study coupled with earlier studies along with a number of citations available in the literature address the repellent nature of deltamethrin.*

Agency Response 15: The reviewer's statement indicating that the study did not supply engorgement or blood feeding data was informational only and not, in and of itself, the reason why the MRID was deemed not acceptable. Rather, the study was not acceptable because assessments did not begin until 2 months after product application. The Agency is unaware of the use of the above definition to describe repellents. This definition is more in line with the term "pesticide" defined in FIFRA 2(u).

Argument 16. *A claim of mosquito repellency has been granted to other generic products currently marketed. As has been discussed earlier the addition of one species of mosquitoes was included to confirm manufacturing had no effect on efficacy and not confirmation of efficacy. Data has been cited and claim should have been granted at the time product was initially registered. The registrant has previously pointed out that Hartz excepted the initial label minus the mosquito claim in an effort to begin state registrations for a 2020 product launch and would again be citing the data to have claim included with repellency claims.*

Agency Response 16: The Agency acknowledges that the Me-Too product (Reg. No. 68451-1) includes repels mosquito claims. As stated above, data must be submitted or cited for the full 6-month timeframe. Addition of the label claim is at the discretion of the Product Manager.

IV. EXECUTIVE DATA SUMMARY:

The status of MRIDs 51018801, 51018802, and 51018803 remain "supplemental." As a standalone study, data do not support claims for mosquito, tick, and flea kill and repellent efficacy. This study should have included data for infestations made no later than 3 days post-collar application. Trials beginning 2 months after application provide insufficient data to add the proposed label claims. For 6-month residual claims, data must be submitted or cited for the full 6-month timeframe. Future submissions should clearly state the registrant's intent.

V. LABEL RECOMMENDATIONS: Refer to the efficacy review dated April 23, 2020 (DP 456609).